Turk J Phys Med Rehab 2022;68(x):i-viii
DOI: 10.5606/tftrd.2022.9596
Available online at www.turkishjournalpmr.com

Original Article

The effect of oral baclofen and botulinum toxin treatments in hemiplegic spasticity on the nociceptive flexor reflex: A randomized clinical trial

Ertürk Güntürk, Halil Ögüt, Hayal Güler, Ayşe Dicle Turhanoğlu

Department of Physical Medicine and Rehabilitation, Hatay Mustafa Kemal University Faculty of Medicine, Hatay, Türkiye

Received: August 16, 2021 **Accepted:** February 15, 2022 **Published online:** August 01, 2022

ABSTRACT

Objectives: This study aimed to analyze the effect of oral baclofen treatment and botulinum toxin type A (BT-A) injection treatment in hemiplegic patients with spasticity on the electromyographic nociceptive flexor reflex (NFR) threshold.

Patients and methods: A total of 29 spastic hemiplegic patients (20 males, 9 females; mean age: 52.9±10.1; range, 27 to 64) with Modified Ashworth Scale (MAS) grades 2-4 were included in the prospective, randomized study between May 2018 and March 2019. The patients were divided into two groups: the BT-A group consisted of 15 patients that underwent a BT-A injection and the baclofen group consisted of 14 patients treated with baclofen. Modified Ashworth Scale, Visual Analog Scale (VAS), Barthel daily life activity index, and NFR threshold values were used in the evaluation of the patients before and after the treatment at the sixth week. The motor evaluation of the patients was performed using Brunnstrom motor staging.

Results: In both groups, MAS and VAS values decreased significantly compared to pretreatment ($p<0.05$). There was a significant decrease in ankle MAS score ($p<0.001$) and a significant increase in Brunnstrom hand recovery stages in the BT-A group compared to pretreatment ($p=0.020$). While the NFR threshold statistically significantly increased in the baclofen group compared to pretreatment ($p=0.007$), there was no significant change in the BT-A group ($p=0.669$).

Conclusion: These results suggest that BT-A injections do not cause a significant change in the NFR threshold in the treatment of spasticity.

Keywords: Baclofen, botulinum toxin type A, electromyography, spasticity, stroke.

Spasticity is frequently observed in patients who have had strokes at the rate of 30 to 80% and causes pain, loss of motor control, and functional insufficiency in patients.[1,2] Spasticity is defined as resistance related to the emergence of hyperactive reflexes that increases in line with speed against passive movements.[3] The specific pharmacological treatments for spasticity are systemic medication containing baclofen, tizanidine, dantrolene sodium, and diazepam, and locally applied botulinum toxin, phenol, and alcohol injections.[4]

Baclofen is β-4-chlorophenyl gamma-aminobutyric acid (GABA) and activates by joining the GABA-B receptor. Through presynaptic GABA-B receptor activation, membrane hyperpolarization and neurotransmitter release decrease. Baclofen's inhibitory effects at the spinal cord level decrease motor neuron and efferent neuron activation. Baclofen decreases monosynaptic reflex activity and, at a smaller rate, polysynaptic reflex activity.[4,5]

Botulinum toxin is a potent neuromuscular blocking agent with its injection in the motor point area inside the muscle. Its primary effect emerges in the motor nerve endpoint. This neurovascular junction blockage results in the chemical denervation of muscle

Corresponding author: Halil Ögüt, MD. Hatay Mustafa Kemal Üniversitesi Tıp Fakültesi, Fiziksel Tıp ve Rehabilitasyon Anabilim Dalı, 31001 Hatay, Türkiye.
e-mail: oguthalil@gmail.com

Cite this article as:
Güntürk E, Ögüt H, Güler H, Dicle Turhanoğlu A. The effect of oral baclofen and botulinum toxin treatments in hemiplegic spasticity on the nociceptive flexor reflex: A randomized clinical trial. Turk J Phys Med Rehab 2022;68(x):i-viii.

fibrils and contraction inefficiency. Botulinum toxin decreases reflex activity in afferent fiber discharge and intrafusal muscle fibrils. In addition, it is efficient in decreasing pain related to spasticity.[5,6]

The nociceptive flexor reflex (NFR), one of the spinal reflexes, is a polysynaptic and multisegmented reflex that protects the body from damaging external stimuli and creates withdrawal in flexor synergies in the stimulated extremity. It is used to evaluate various methods of processing pain and pain pathways at the spinal and supraspinal levels and evaluated objectively through electrophysiological measurement.[7] When functional losses are taken into consideration in stroke patients, this protective reflex gains importance. Medication used in spasticity treatment may lead to changes in spinal and supraspinal reflex regulation and neuronal connections, influence NFR response, and leave the body vulnerable to damaging external stimuli. There is a small number of studies in the literature in which the effect of spasticity medication on the NFR threshold is evaluated.[8-10] Taking baclofen's capacity to decrease monosynaptic activity and, to a lesser degree, polysynaptic reflex activity and botulinum toxin's capacity to decrease reflex activity in afferent fiber discharge and intrafusal muscle fibrils with its paralysis as the starting point, we aimed to electromyographically measure the effect of these medications in hemiplegia patients with spasticity on NFR threshold.

PATIENTS AND METHODS

A total of 29 patients (20 males, 9 females; mean age: 52.9±10.1; range, 27 to 64) who developed spastic hemiplegia as a result of embolism or hemorrhage with Modified Ashworth Scale (MAS) grades 2-4 and applied to the Physical Medicine and Rehabilitation Polyclinic of the Hatay Mustafa Kemal University Faculty of Medicine between May 2018 and March 2019 were included in the prospective, randomized study. The patients were randomized into two groups: the botulinum toxin type A (BT-A) group (n=15), which underwent BT-A injections, and the baclofen group (n=14), which received baclofen treatment. The study flowchart is presented in Figure 1.

Individuals who had received botulinum toxin injection treatment in the past six months, patients receiving oral antispastic treatment, individuals who have an allergy and hypersensitivity story related to the medication to be used, individuals who had diseases that might cause neuropathy or used medication and substances that might cause neuropathy in their medical history, individuals with hematoma, infections or skin lesions in the planned injection area, hemorrhage disorders, joint contracture, and patients who were MAS Grade 1 were excluded from the study.

The patients' sex, age, weight, height, cerebrovascular case etiology, symptom durations and hemiplegic sides were recorded. The MAS

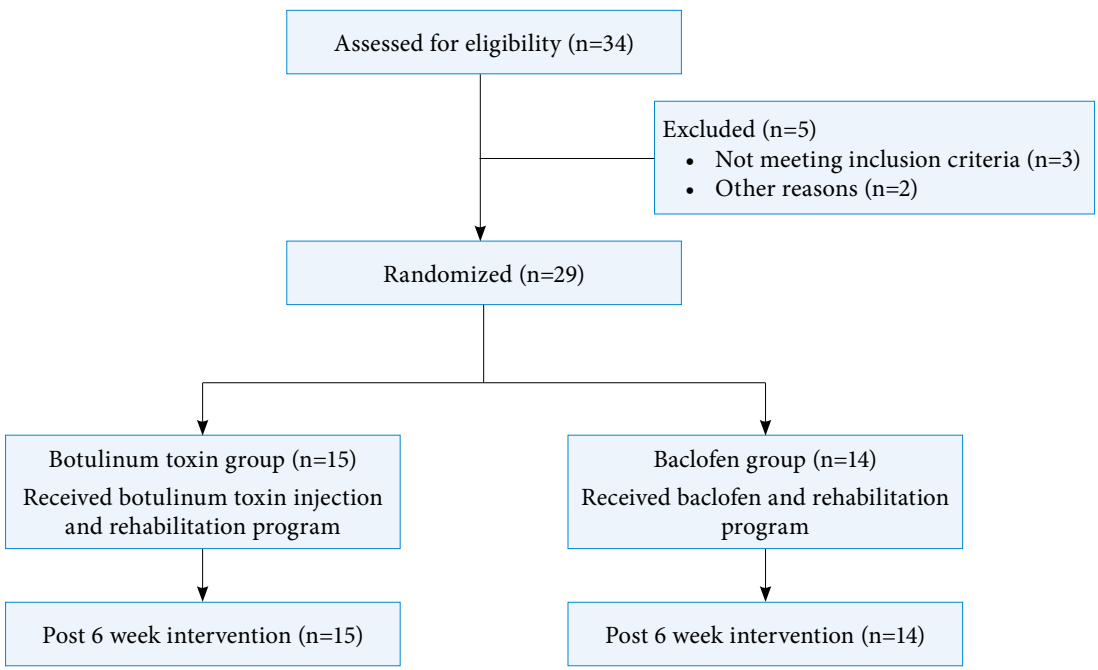

Figure 1. Study flowchart.

was used to evaluate spasticity intensity. The MAS grading was done as 1, 1+, 2, 3, and 4, and it was successively graded as 1, 2, 3, 4, and 5 for the statistical analysis. The motor evaluation of the patients was performed using Brunnstrom motor staging in the upper extremity, hand, and lower extremity. A 10 cm long Visual Analog Scale (VAS) was used to evaluate the hemiplegic side pain of the patients. The daily life activities of the patients were evaluated with the Barthel index.[11] The Barthel index consists of 10 questions, and the highest total score that can be received is 100. The NFR threshold value measurement was performed with electromyography on the unaffected lower extremities of the patients.[12] The electrical stimulations were given with a bipolar stimulator from the sural nerve near the side of the lateral malleolus. To achieve a threshold value, the electrical stimulation was started from 0 mA and increased in 4 mA intervals until a NFR response was achieved. After the initial NFR response was achieved, the stimulation intensity was decreased in 2 mA intervals until the response disappeared. Afterward, the stimulation intensity was arranged with high and low stimulations of 1 mA until a stabile NFR response was achieved. The stable NFR threshold value achieved in this manner was recorded. The electrical stimulation intensity, which made it possible for the NFR threshold response to be achieved, was recorded in mA. Prior to the treatment and at the sixth week, which was the end of treatment, MAS, Brunnstrom stages, VAS values, Barthel daily life activity index, and electromyographic NFR thresholds of all patients were recorded.

The 15 patients in the first group were injected with BT-A under ultrasonography guidance in their upper and lower extremity muscles that scored ≥2 according to MAS in suitable dosages according to the predetermined dosage diagram (total dosage of 100-300 IU). The 14 patients in the second group were given 5 mg of oral baclofen twice daily as the initial dosage starting from the first day. This was increased by 5 mg every five to seven days up to 80 mg until the effective antispasticity dosage was achieved (total dosage of 30-80 mg). The dosage was not increased anymore since the patients were not able to tolerate higher dosages. Both patient groups exercised a physical therapy and rehabilitation program together with antispastic treatment. In the rehabilitation procedure, positioning, joint range of motion and stretching exercises, strengthening exercises, balance and coordination, ambulation exercises, hot or cold compress, and functional electrical stimulation treatments were applied to each patient for 60 min. The treatment program was applied by the same physiotherapist five times a week, once a day for six weeks.

Statistical analysis

The sample size calculation was performed using the G*Power version 3.1.9.2 software (Heinrich-Heine-Universität, Düsseldorf, Düsseldorf, Germany). The effect size was calculated as 1 using the mean NFR thresholds from healthy volunteers using the difference between two independent means in accordance with Bossard et al.'s[12] study. For a statistical power of 0.80 and an alpha (α) level of 0.05, a sample size of 34 patients (17 participants in each group) was required. In the power analysis performed at the end of the study using NFR threshold values, the power of this study, which included 29 patients, was found to be 74%. All obtained data were analyzed with IBM SPSS version 21.0 software (IBM Corp., Armonk, NY, USA). Frequency (%) and median (minimum and maximum) were used for descriptive statistics. The mean and standard deviation values were expressed as mean± standard deviation (SD). The data obtained through the measurements were separately evaluated in each group with the Shapiro-Wilk test in terms of normal distribution. In the comparison of values that did not display normal distribution, nonparametric tests were used. While the Mann-Whitney U test was used in the comparison of the two groups, the Wilcoxon signed ranks test was used within the same group prior to and after comparisons. A p value of <0.05 was considered statistically significant.

RESULTS

The mean age of the 15 patients in the BT-A group was 52.4±13.5 (median 58; range, 27 to 64) years, and the mean age of the patients in the baclofen group was 53.4±5.1 (median, 55; range, 41 to 60) years. There was no statistically significant difference between the groups (p>0.05). There was no statistically significant difference between the groups in terms of age, sex, height, weight, disease duration, and disease etiology (p>0.05). The demographic data of 29 patients who participated in the study are summarized in Table 1.

In the BT-A and baclofen groups, a statistically significant decrease was observed after the treatment in the elbow, wrist, finger, knee, and ankle MAS parameters compared to prior to the treatment (p<0.05). A statistically significant difference was determined in favor of the BT-A group in the ankle MAS value after

TABLE 1
Comparison of demographic data of patients

	BT-A group (n=15)				Baclofen group (n=14)				
	n	%	Median	Min-Max	n	%	Median	Min-Max	*p*
Age (year)			58	27-64			55	41-60	0.168†
Height (cm)			170.0	155.0-178.0			169.5	160.0-175.0	0.335†
Weight (kg)			76.0	55.0-85.0			72.0	62.0-81.0	0.190†
Sex									0.700*
Male	11	55			9	45			
Female	4	44.4			5	55.6			
Disease duration (month)			20	6-57			23	16-55	0.844†
Etiology									0.812‡
Ischemia	9	60			9	64.3			
Hemorrhage	6	40			5	35.7			

* Fisher exact test; † Mann-Whitney U test; ‡ Chi-square.

TABLE 2
Comparison of the MAS and Brunnstrom values of the groups

	BT-A group (n=15)		Baclofen group (n=14)		
	Median	Min-Max	Median	Min-Max	*p**
Elbow MAS					
Before	3.00	2.00-4.00	2.50	2.00-3.00	0.176
After	2.00	2.00-3.00	2.00	1.00-2.00	0.083
p	0.003†		0.003†		
Wrist MAS					
Before	3.00	2.00-4.00	3.00	2.00-4.00	0.639
After	2.00	2.00-3.00	2.00	2.00-3.00	0.508
p	0.004†		0.002†		
Fingers MAS					
Before	3.00	2.00-4.00	3.00	2.00-4.00	0.795
After	2.00	1.00-3.00	2.00	2.00-3.00	0.386
p	0.004†		0.001†		
Knee MAS					
Before	2.00	1.00-3.00	2.00	1.00-3.00	0.758
After	2.00	1.00-2.00	1.00	1.00-2.00	0.349
p	0.024†		0.004†		
Ankle MAS					
Before	3.00	3.00-4.00	3.00	2.00-4.00	0.089
After	2.00	1.00-3.00	3.00	2.00-4.00	0.025*
p	<0.001†		0.025†		
Upper extremity Brunnstrom					
Before	3.00	2.00-5.00	3.00	2.00-4.00	0.502
After	4.00	2.00-5.00	3.50	2.00-4.00	0.512
p	0.083		0.083		
Hand Brunnstrom					
Before	3.00	2.00-5.00	3.00	2.00-4.00	0.727
After	4.00	3.00-5.00	3.00	3.00-4.00	0.294
p	0.020†		0.083		
Lower extremity Brunnstrom					
Before	3.00	2.00-4.00	3.00	2.00-4.00	0.531
After	4.00	3.00-4.00	3.00	2.00-4.00	0.158
p	0.059		0.157		

BT-A: Botulinum toxin type A; MAS: Modified Ashworth Scale; * Mann-Whitney U test; † Wilcoxon Signed Rank test.

TABLE 3
Comparison of VAS, Barthel, and NFR values of the groups

	BT-A group (n=15)		Baclofen group (n=14)		
	Median	Min-Max	Median	Min-Max	*p**
Rest VAS					
Before	3.00	2.00-5.00	3.00	2.00-4.00	0.426
After	2.00	1.00-4.00	2.00	1.00-3.00	0.538
p	0.004†		0.001†		
Movement VAS					
Before	4.00	3.00-7.00	4.00	3.00-5.00	0.272
After	3.00	2.00-5.00	3.00	2.00-4.00	0.544
p	0.001†		0.001†		
Barthel					
Before	50.00	20.00-85.00	50.00	30.00-65.00	0.676
After	55.00	25.00-85.00	50.00	30.00-65.00	0.567
p	0.059		0.157		
NFR					
Before	8.10	4.20-12.00	8.10	4.20-10.20	0.887
After	8.10	4.20-12.00	10.00	4.20-12.00	0.121
p	0.669		0.007†		

VAS: Visual Analog Scale; NFR: Nociceptive flexor reflex; * Mann-Whitney U test; † Wilcoxon Signed Rank test.

the treatment (p<0.001). While a significant increase was observed in the BT-A group after the treatment in Brunnstrom hand stages (p=0.020), there was no significant difference in the baclofen group (p=0.083; Table 2).

The groups' VAS resting and movement parameters were significantly low after the treatment (p<0.05), and there was no difference between the groups (p>0.05). A significant difference was not found in the NFR threshold in the BT-A group compared to baseline (p=0.669). In the baclofen group, the NFR threshold statistically significantly increased after the treatment (p=0.007; Table 3).

DISCUSSION

We analyzed the effect of BT-A and baclofen treatment on the NFR threshold in spastic hemiplegia patients. The NFR threshold increased in the baclofen group, whereas a significant change was not observed in the NFR threshold in the BT-A group. The MAS and VAS showed a significant improvement in the condition of the patients in both baclofen and BT-A groups. A significant difference was observed in ankle spasticity in favor of the BT-A group. In terms of Brunnstrom upper extremity, hand, and lower extremity stages, a statistically significant increase was found in the hand stages of the BT-A group. The increase observed in Brunnstrom stages in the baclofen group was not statistically significant.

In this study, while baclofen led to a significant increase in the NFR threshold in hemiplegic patients, BT-A did not cause any change in this threshold. In a previous study by Parise et al.[9] on 17 spastic patients, it was found that flexor reflex amplitude decreased and reflex threshold increased after the baclofen treatment. Milanov[8] showed in their study involving 30 spastic hemiplegic patients that flexor reflex increased and duration of latency decreased after baclofen treatment. It was observed in this study that the NFR threshold value significantly increased after the treatment compared to the initial stages in the group that was given baclofen treatment. The main role of the flexion reflex, also known as the withdrawal reflex, is to protect the organism against stimuli that might be damaging by withdrawing the limb.[13] Therefore, it should be kept in mind that this protective reflex might decrease in hemiplegic patients who receive this antispastic treatment. This,

in turn, might leave patients vulnerable to external stimuli. Protective strategies might be included in the rehabilitation of patients in this group who receive antispastic treatment. In addition, patients needed to be trained to minimize possible damages they might experience in their daily life activities.

Taira et al.[14] have analyzed the effect of baclofen treatment in 14 patients with central pain who have had strokes and spinal cord injuries. The study indicates that allodynia and hyperalgesia conditions regressed after the baclofen treatment. The results showed that the dysfunction of GABAergic systems plays a role in the pathophysiology of central pain. Baclofen is a GABA-B receptor agonist, causing the inhibition of calcium conductivity over the voltage-gated calcium channels and leading to membrane hyperpolarization by increasing potassium conductivity. This explains how baclofen reduces the release of excitatory neurotransmitters.[15] The change in NFR, which takes place after the use of substances with analgesic efficiency, has been shown in many studies. Bossard et al.[12] observed that the NFR threshold value increased after the patients were given morphine, an analgesic. In the present study, we found that NFR thresholds increased and patients' pain scales decreased after baclofen treatment.

It has been shown in studies on animals injected with BT-A that motor neurons have gone through retrograde axonal transport.[16] In Aymard et al.'s[17] study, it was shown that BT-A blocks Renshaw cells and can help reactivate reciprocal Ia interneurons and improve reciprocal inhibition. This shows that BT-A induces spinal plasticity, which allows reciprocal inhibition to be regained. A change in the NFR threshold can be expected through these mechanisms with BT-A application. However, while baclofen increased this threshold, BT-A did not cause any difference in this study. There is a small number of studies in which NFR is evaluated after BT-A treatment. In Alvisi et al.'s[10] study, upper extremity basal electromyography (EMG) activity and NFR amplitude were evaluated after BT-A application in the subacute phase of a stroke. After the treatment, the decrease in amplitude related to NFR and changes in basal EMG activity were observed. A decrease in EMG amplitude was observed in some upper extremity muscles to which BT-A was not injected, and it was stated that this might be due to the toxin's retrograde effect.

In pain management, botulinum toxin decreases muscle hyperactivity and displays an analgesic effect. However, the latest studies show that this neurotoxin might directly have analgesic mechanisms different from its neuromuscular effects. In studies on animals, it has been shown that BT-A causes the release of substance P, which is one of the dorsal root ganglion neurons, and reduces the release of calcitonin gene-related peptide in trigeminal ganglion neurons. In addition, it has been shown in animal studies that subcutaneous BT-A injections can reduce harmful stimulus-induced inflammation, reduce glutamate secretion in the axon of the nociceptor, and decrease the activity of spinal dorsal root neurons. These findings show that BT-A's nerve transmission suppresses the release of neurotransmitters which affect peripheral and central sensitizations and directly affect the nociceptors.[18] Botulinum toxin type A's retrograde axonal transport in rats has been verified by showing the existence of the BT-A breakdown product cl-SNAP-25, which is localized together with TRPV1 in the ipsilateral dorsal root ganglion.[19] We would expect BT-A to cause a change in the NFR threshold, but we did not see such a change in this study. We think that further studies are needed to explain the suppressing effect of BT-A on pain receptors.

In Demiryürek and Gündoğdu[20] study using BT-A on spastic patients who have had strokes, a statistically significant decrease was found in the first-and third-month VAS values compared to prior to the study. Ucar et al.,[21] in their study on 30 patients with spasticity, found a significant decrease in the VAS value after intrathecal baclofen treatment. In a study of 273 patients with spasticity related to stroke, it was determined that the VAS scores significantly decreased compared to the placebo group after BT-A injection, and the decrease in pain lasted up to 58 weeks.[22] Similar to the literature, we also found a significant decrease in VAS-rest and VAS-movement values measured after the treatment in both groups compared to prior to the study. We think that besides the medical treatments given to the patients included in the study, physical therapy and rehabilitation contributed to the decrease in VAS scores as well.

In this study, a difference was found after the treatment in ankle MAS value in favor of the BT-A group, and this difference was statistically significant. Bakheit et al.[23] found in their study in which placebo and BT-A were compared in upper extremity spasticity after stroke that there was a significant decrease in the wrist and finger MAS values at the fourth week. Kaji et al.[24] did a placebo-controlled study with BT-A in lower extremity spasticity after stroke. The researchers found a significant decrease in the ankle MAS value

with BT-A application at the four, six, and eight weeks compared to placebo.

In a study involving 16 hemiplegic patients with upper and lower extremity spasticity, a nonsignificant increase was found after BT-A treatment at the sixth week in the upper and lower extremity Brunnstrom stages.[25] In this study, while the increase in Brunnstrom hand stages was significant in the group receiving BT-A treatment, it was not significant in the upper and lower extremity stages. There was no significant change in Brunnstrom stages in the group receiving baclofen treatment.

Spasticity frequently causes difficulties in daily life activities. Demiryürek and Gündoğdu,[20] in their study on BT-A in spastic patients who have had strokes, found a statistically significant increase in the Barthel score at one and three months compared to prior to the treatment. Bakheit et al.[23] did not find any significant improvement in the Barthel score at the fourth week in spastic patients after the BT-A treatment compared to placebo. The difference between the studies may be that the Barthel score has evaluated functions such as urinary incontinence and bowel control, which are not affected by the treatment of localized muscle spasticity. We observed an increase in the Barthel score in both groups, although it did not reach a statistically significant level.

This study has some limitations. First, the fact that the number of patients who completed the study was less than planned reduces the power of the study. Second, due to technical conditions (a stable NFR threshold value could not be recorded from spastic muscles), the NFR threshold value was recorded from a muscle that did not receive a BT-A injection.

In conclusion, BT-A and baclofen treatment combined with rehabilitation in hemiplegic patients can contribute to the functional recovery of patients. Botulinum toxin type A treatment having no effect on the NFR threshold, causing a significant increase in Brunnstrom hand stages, and being more effective in terms of ankle spasticity compared to baclofen treatment may mean that the local treatment application is superior to oral baclofen treatment.

Ethics Committee Approval: The study protocol was approved by the Hatay Mustafa Kemal University Faculty of Medicine Ethics Committee (no: 2018/159). The study was conducted in accordance with the principles of the Declaration of Helsinki.

Patient Consent for Publication: A written informed consent was obtained from each patient.

Data Sharing Statement: The data that support the findings of this study are available from the corresponding author upon reasonable request.

Author Contributions: Concept, design, materials, data collection, critical review: E.G.; materials, analysis, literature review, writing the article, critical review: H.O.; design, analysis, literature review, critical review: H.G.; design, data collection, literature review, writing the article, critical review: A.D.T.

Conflict of Interest: The authors declared no conflicts of interest with respect to the authorship and/or publication of this article.

Funding: The authors received no financial support for the research and/or authorship of this article.

REFERENCES

1. Malhotra S, Cousins E, Ward A, Day C, Jones P, Roffe C, et al. An investigation into the agreement between clinical, biomechanical and neurophysiological measures of spasticity. Clin Rehabil 2008;22:1105-15.
2. Watkins CL, Leathley MJ, Gregson JM, Moore AP, Smith TL, Sharma AK. Prevalence of spasticity post stroke. Clin Rehabil 2002;16:515-22.
3. Mukherjee A, Chakravarty A. Spasticity mechanisms - for the clinician. Front Neurol 2010;1:149.
4. Thibaut A, Chatelle C, Ziegler E, Bruno MA, Laureys S, Gosseries O. Spasticity after stroke: Physiology, assessment and treatment. Brain Inj 2013;27:1093-105.
5. Yan X, Lan J, Liu Y, Miao J. Efficacy and safety of botulinum toxin type A in spasticity caused by spinal cord injury: A randomized, controlled trial. Med Sci Monit 2018;24:8160-71.
6. Andringa A, van de Port I, van Wegen E, Ket J, Meskers C, Kwakkel G. Effectiveness of botulinum toxin treatment for upper limb spasticity poststroke over different ICF domains: A systematic review and meta-analysis. Arch Phys Med Rehabil 2019;100:1703-25.
7. Sandrini G, Serrao M, Rossi P, Romaniello A, Cruccu G, Willer JC. The lower limb flexion reflex in humans. Prog Neurobiol 2005;77:353-95.
8. Milanov IG. Flexor reflex for assessment of common interneurone activity in spasticity. Electromyogr Clin Neurophysiol 1992;32:621-9.
9. Parise M, García-Larrea L, Mertens P, Sindou M, Mauguière F. Clinical use of polysynaptic flexion reflexes in the management of spasticity with intrathecal baclofen. Electroencephalogr Clin Neurophysiol 1997;105:141-8.
10. Alvisi E, Serrao M, Conte C, Alfonsi E, Tassorelli C, Prunetti P, et al. Botulinum toxin A modifies nociceptive withdrawal reflex in subacute stroke patients. Brain Behav 2018;8:e01069.
11. Küçükdeveci AA, Yavuzer G, Tennant A, Süldür N, Sonel B, Arasil T. Adaptation of the modified Barthel Index for use in physical medicine and rehabilitation in Turkey. Scand J Rehabil Med 2000;32:87-92.

12. Bossard AE, Guirimand F, Fletcher D, Gaude-Joindreau V, Chauvin M, Bouhassira D. Interaction of a combination of morphine and ketamine on the nociceptive flexion reflex in human volunteers. Pain 2002;98:47-57.
13. Ertekin C, editor. Central and Peripheral EMG. 1st ed. İzmir: İstanbul Kitabevi; 2006.
14. Taira T, Kawamura H, Tanikawa T, Kawabatake H, Iseki H, Ueda A, et al. A new approach to the control of central deafferentation pain--spinal intrathecal baclofen. Acta Neurochir Suppl 1995;64:136-8.
15. Slonimski M, Abram SE, Zuniga RE. Intrathecal baclofen in pain management. Reg Anesth Pain Med 2004;29:269-76.
16. Caleo M, Restani L. Direct central nervous system effects of botulinum neurotoxin. Toxicon 2018;147:68-72.
17. Aymard C, Giboin LS, Lackmy-Vallée A, Marchand-Pauvert V. Spinal plasticity in stroke patients after botulinum neurotoxin A injection in ankle plantar flexors. Physiol Rep 2013;1:e00173.
18. Sim WS. Application of botulinum toxin in pain management. Korean J Pain 2011;24:1-6.
19. Fan C, Chu X, Wang L, Shi H, Li T. Botulinum toxin type A reduces TRPV1 expression in the dorsal root ganglion in rats with adjuvant-arthritis pain. Toxicon 2017;133:116-22.
20. Demiryürek BE, Gündoğdu AA. İnme sonrası spastisite tedavisinde botulinum toksin enjeksiyonu etkinliğinin değerlendirilmesi. Türk Nöroloji Dergisi 2017;23:15-20.
21. Ucar T, Kazan S, Turgut U, Samanci NK. Outcomes of intrathecal baclofen (ITB) therapy in spacticity. Turk Neurosurg 2011;21:59-65.
22. Wissel J, Ganapathy V, Ward AB, Borg J, Ertzgaard P, Herrmann C, et al. OnabotulinumtoxinA improves pain in patients with post-stroke spasticity: Findings from a randomized, double-blind, placebo-controlled trial. J Pain Symptom Manage 2016;52:17-26.
23. Bakheit AM, Pittock S, Moore AP, Wurker M, Otto S, Erbguth F, et al. A randomized, double-blind, placebo-controlled study of the efficacy and safety of botulinum toxin type A in upper limb spasticity in patients with stroke. Eur J Neurol 2001;8:559-65.
24. Kaji R, Osako Y, Suyama K, Maeda T, Uechi Y, Iwasaki M; GSK1358820 Spasticity Study Group. Botulinum toxin type A in post-stroke lower limb spasticity: A multicenter, double-blind, placebo-controlled trial. J Neurol 2010;257:1330-7.
25. Atalay N, Akkaya N, Özlü A, Sahin F. The efficacy of Botulinum Toxin A in poststroke spasticity. Anatolian Journal of Clinical Investigation 2012;6:92-6.